SCIENTIFIC RESEARCH

VALUATION OF THE CT LI-RADS TREATMENT RESPONSE V2018 IN PATIENTS AFTER FIRST-LINE DEB-TACE) FOR HEPATOCELLULAR CARCINOMA (HCC)

Le Duc Nam *, Vu Le Minh **, Ngo Le Lam**, Bui Van Giang ***, Nguyen Quoc Dung*.***

SUMMARY

Background: In hepatocellular carcinoma (HCC), locoregional therapy (LRT) included transarterial chemotherapy embolization - TACE is performed as a bridging or downstaging treatment, improved overall survival, or a curative treatment. Liver Imaging Reporting and Data Systems (LI-RADS) Treatment Response was created to evaluate each lesion post-TACE, which has localized and is suitable for determining whether the tumor is still viable or non-viable.

Purpose: To evaluate the application of the Liver Imaging Reporting and Data System (LI-RADS) treatment response algorithm (LR-TR) on CT in patient post-treatment evaluation following drug-eluting beads transarterial chemoembolization (DEB-TACE) for hepatocellular carcinoma (HCC).

Materials and Methods: Between 6/2021 and 9/2022, a prospective and retrospective cross-sectional study involved 29 patients with hepatocellular carcinoma (HCC) who underwent treatment-based drug-eluting beads transarterial chemoembolization (DEB-TACE). The clinical situation, AFP levels, and Computer tomography of the patient after treatment were analyzed.

Results: a total of 29 patients with a median age was 61,3 ± 11.03 years old, male to female ratio was 13.5 : 1. After first-line DEB-TACE: the performance status response were improved in 28/29 patient, AFP response in 31%, LR-TR non-viable in 13 (44.8%) of 29 patients. The performance status response- AFP response- imaging response correlation was not statistically different with p= 0.552 and p=0.647.

Conclusion: Using CT LR-TR to evaluate HCC post-DEB-TACE was an easy-to-use means, suitable for clinical practice, and useful for vascular interventionalist.

Keywords: *hepatocellular carcinoma, transarterial chemotherapy embolization, treatment response, LI-RADS treatment response.*

**Radiology Department-Frienship Hospital*

*** Radiology Department-VietNam National Cancer Hospital*

**** College of Health science-VinUni*

***** Radiology Center-Medlatec Hospital*

I. INTRODUCTION:

According to BCLC (Barcelona Clinic Liver Cancer), transarterial chemoembolization - TACE is indicated for patients with intermediated-stage, unresectable tumors, in patients with well-preserved liver function PS 0-2, to control tumor growth, improving overall survival [1]. Transarterial chemoembolization with drug-eluting beads (DEB-TACE) is both embolization and slow and sustained release, therefore it has been shown in several randomized controlled clinical trials to be more effective and less adverse than conventional TACE [2]. Evaluation of the treatment response of HCC following TACE is important in determining the next treatment plan for the patient. The LI-RADS 2018 includes an additional classification for treatment response of HCC by CT scans or MRI, which is an update with clinical practice guidelines of the American Association for the Study of Liver Diseases - AASLD), evaluates each lesion post-TACE, which has localized and suitable for determining whether the tumor is still viable or non-viable [3]. Up to now, Vietnam has not had a research topic on this issue, so we do research with the goal *"Study on the value of the LI-RADS 2018 on CT scans to evaluate treatment responses of hepatocellular carcinoma post transarterial chemoembolization with drug-eluting beads".*

II. MATERIALS AND METHODS

1. Materials: A total of 58 patients were diagnosed with HCC and underwent chemoembolization at K Tan Trieu Hospital and Huu Nghi Hospital during the period from June 2021 to September 2022, including 29 patients underwent treatment base drug-eluting beads transarterial chemoembolization.

Patient inclusion criteria: Patients with the definitive diagnosis of HCC and underwent treatment base drug-eluting beads transarterial chemoembolization, had CT scans before and after the first embolization 1-3 months.

Patient elimination

- Patients are receiving or have previous systemic treatment.

- Patients did not have CT scans or unsatisfactory CT images before and after the intervention.

- Patients were diagnosed with Infiltrative Hepatocellular Carcinoma.

- Patients had severe coagulopathy: platelets <50 G/l, prothrombin <60 %.

- Patients presented with Hepatic encephalopathy, rapidly relapsing ascites, and bleeding due to esophageal varices.

- Patients got an allergy to contrast materials, and hepatic embolization agents.

- Patients unfollowed routine follow-ups.

- Patients did not agree to participate in the study.

2. Methods: prospective and retrospective cross-sectional study

3. *Research procedures:*

Prepare the patient: clinical examination and AFP test.

Multi-slide computed tomography before embolization supported by the American College of Radiology (ACR) 2018 [3]: Non-enhanced CT, arterial phase 30-45 seconds post-injection, portal venous phase 70 - 90 seconds post-injection, delayed phase 2 - 5 minutes post-injection.

Transarterial chemoembolization technique:

- Access femoral artery by 6F Sheath according to Seldinger technique, celiac trunk angiography, superior mesenteric angiography by Yashiro catheter (5Fr or RH 5F)

- Approach by Progreat Micro catheter (1.98 F, 2.0 F, 2.4 F, 2.6 F, 2.7 F) to feeding artery to the tumor, evaluation of the source of the feeding artery to the tumor in detail. The catheter stops before the first feeding artery to the tumor. In case embolize right/left hepatic arteries, ensure that the catheter tip passes the extrahepatic arterial origin.

- In case of multiple tumors, select the target tumor for intervention and compare it with CT scans

- DEB-TACE until the flow stops, stop for 5 minutes and check the flow, then stop DEB-TACE if no flow or reflux.

- Evaluate the results of embolization with the Yashiro 5F catheter in the celiac truck and remove the catheter.

The process of evaluating the effectiveness after the first embolization is 1-3 months:

- Clinical examination to evaluate the patient's overall condition according to the PTS scale or rank good - same - poor.

- AFP test.

- Liver CT scans evaluate tumor changes, recurrence, and extrahepatic metastases.

- Evaluation following DEB-TACE for HCC by LR-TR scale on CT scans

Table 1. *LR-TR classification for HCC treatment response.*

LR-TR non-evaluable	After treatment, the response could not be assessed due to noisy or damaged images
LR-TR nonviable	After treatment, it is unlikely or completely nonviable
LR-TR equivocal	After treatment, equivocal viable
LR-TR viable	High possibility or sure viable

* **Source**: Chernyak (2018) [3]

Statistics: Variables were collected and analyzed with SPSS 20 software. Compare the ratio characteristics of the study group base Chi-Squared test or Fisher's Exact Test.

III. RESULTS

A total of 58 patients were diagnosed with HCC and underwent chemoembolization at K Tan Trieu Hospital and Huu Nghi Hospital during the period from June 2021 to September 2022, including 29 patients underwent treatment base drug-eluting beads transarterial chemoembolization:

Table 2. *Age and gender characteristics of the study subjects*

Age, gender		n	%
Range	18-39	1	3,4
	40-60	11	37,9
	> 60	17	58,6
	Total	29	100
Median	61,3 ± 11.03 (Age range 35-82 years old)		
Gender	Male	27	93.1
	Female	2	6.9
	Total	29	100

Comments: Median age is 61,3 ± 11.03 (Age range 35-82 years old), and the most common age group is over 60 years old (58,6%). Male accounted for 93,1%, male/female = 13.5/1.

Table 3. *Serum AFP test before treatment*

AFP subgroup	n	%
Normal (< 20ng/ml)	12	41,4
20 - 400 (ng/ml)	8	27,6
> 400 ng/ml	9	31

Comments: 17 patients (58,6%) increase AFP before treatment.

Table 4. *Tumor characteristics before treatment*

Tumor characteristics on CT scans		n	%
Location	Subsegment	18	62,1
	Segment	5	17,2
	2 segment	6	20,7
	>2 segment	0	0
Amount of tumors	1 tumor	14	48,3
	2 tumors	9	31
	≥ 3 tumors	6	20,7
Morphology	Mass nodule	14	48,3
	Mass with peripheral nodule	11	37,9
	Mass multiple nodules	4	13,8
Source of feeding vessels to the tumor	Intrahepatic	23	79,3
	Extrahepatic	2	6,9
	Both	4	13,8
Arteriovenous fistula inside the tumor	0	23	79,3
	1	6	20,7
Portal vein thrombosis	Yes	0	0
	No	29	100
Diameter range (cm)	≤ 5	16	55,2
	5-8	7	24,1
	> 8	6	20,7
Diameter median(cm)	6,04 ± 3,13 (lowest 2,1 và highest 16,5)		

Comments: Commonly, patients have 01 tumor (48.3%), the diameter median is about 6 cm, most of the tumors are < 5 cm in size with 55.2%, usually located in one subsegment (62.1%) with mass nodules which often met (48.3%), is fed mainly by the intrahepatic artery (79.3%), very little is seen the arteriovenous fistula and portal vein thrombosis.

Table 5. *Patient pre-treatment distribution by BCLC stage, Child-Pugh score, and PS*

Characteristic	%
Child-Pugh	
A	28 (96,6 %)
B	1 (3,4%)
C	0
PS	
0	9 (31%)
1	20 (69%)
BCLC stage	
A	13 (44,8%)
B	16 (55,2%)

Most patients had Child-Pugh A cirrhosis (96,6%), and all patients in the study had BCLC stage A and B cirrhosis, over half of the patients had BCLC stage B cirrhosis (55,2%).

Table 6. *The rate of LR-TR*

	n	%
LR-TR Non-viable	12	41,4
LR-TR Viable	17	58,6
Total	29	100

The rate of LR-TR non-viable was 41.4% (12/29), LR-TR viable was 58.6 %(17/29)

Table 7. *The correlation between LR-TR and pre-treatment HCC characteristics on CT*

Characteristic \ LR-TR		Non-Viable	Viable	p*	r
Location	Sub-Segment	11	7	0,018	0,527
	Segment	1	4		
	2 Segment	0	6		
	> 2 Segment	0	0		
Morphological HCC	Simple nodular type	9	5	0,056	
	Simple nodular type with extra-nodular growth type	2	9		
	Confluent multinodular type	1	3		
Measurement	≤5cm	10	6	0,022	0,476
	>5cm	2	11		

* Fisher's exact test

The relationship between LR-TR and tumor localization and measurement was an average correlation coefficient (p=0.018 and p=0.022, r=0.527 and r=0.476). The relationship between LR-TR and tumor morphology was not significant (p=0.056).

Table 8. *The correlation between LR-TR and the level of embolization*

Lobe		level of embolization				p*	correlation coefficient
		Selective	Super-selective	Ultra-Selective			
LR-TR	Non-viable	0	2(22,2%)	10(55,6%)	0	0,187	
	Viable	2(100%)	7(77,8%)	8(44,4%)	0		

* Fisher's exact test

The relationship between LR-TR and the level of embolization was not significant, p=0.187

Table 9. *Treatment response*

Characteristic		LI-RADS v2018 treatment response algorithm			P (Fisher's exact test)
		Non-viable	Viable		
Clinical response	Responded	13	15	28	0,552
	No	0	1	1	
Total		13	16	29	
AFP	Responded	4	5	9	0,647
	No	9	11	20	
Total		13	16	29	

The most of patients had clinical improvement with 28/29 patients, and 9 patients (31%) had AFP responded after treatment. On the other hand, there was no significant difference in clinical response, and AFP response between LI-RADS non-viable and LI-RADS viable (p = 0.552 and p = 0.647, respectively).

IV. DISCUSSION

According to the practice guidance by the American Association for the study of Liver Diseases, there are two available therapeutic options: curative and noncurative interventions. Transarterial chemoembolization - TACE is a noncurative intervention, including conventional TACE and Drug-eluting bead TACE (Deb-TACE). According to the BCLC system, TACE is the treatment for patients who have intermediate-stage tumors, limited unresectable multinodular lesions, and well-preserved liver function (PS 0-2) to control tumor growth, increasing the survival time.[1] In patients with resectable HCC, TACE is also used to reduce HCC recurrence and combine with Portal Vein Embolization (PEV) to ensure the volume of the remaining liver [4].

Of 29 patients who underwent DEB-TACE in our study, the mean age of patients was 61.3 years, and 27 (91.8%) patients were male individuals, this result is similar to other studies in Vietnam. That shows the limited screening for early diagnosis of HCC in Vietnam.

AFP is the tumor biomarker used for the early diagnosis of HCC and elevates the treatment response. Normally, AFP concentration is less than 20ng/ml, the high AFP concentration of more than 400 ng/ml is a criterion for HCC diagnosis. In our study, 17 patients (58,6%) have increased AFP, similar to some other domestic and foreign authors [5].

The evaluation of the treatment response algorithm after TACE is based on size, lesional enhancement, recurrence lesion, and the presence of vascular invasion. The treatment response levels have prognostic value in survival in HCC. In patients with unresectable HCC, TACE has been shown to prolong survival as well as improve clinical symptoms. This result is achieved by controlled tumor growth and reduction in tumor size leading to a decrease in intrahepatic mass effect and improved liver function. In our study, all (29) patients had good treatment responses.

After treatment by transarterial or percutaneous interventions, the necrotic area of the tumor is more interesting than the reduced tumor size, but the lipiodol accumulation in tumors after cTACE limits the assessment of the necrotic area. In our study, we used Liver Imaging Reporting and Data System (LI-RADS) treatment response algorithm (LR-TR) version 2018, on the initial post-treatment CT. The LI-RADS TRA not only recognized arterial phase hyperenhancement, but also included the appearance of washout lesions in the ventral and late phase, and enhancement patterns similar to pretreatment imaging, this is consistent with the pathological HCC because the blood supply for HCC not only the arterial but also the portal vein which increases the sensitivity for the evaluated treatment respons [6]. The LI-RADS TRA is used to assess response after local-regional therapy, which includes ethanol and radiofrequency or

microwave ablation, transarterial chemoembolization or radioembolization, and external beam radiation therapy. The algorithm also applies to observations at the surgical margin after resection of HCC and is evaluated similarly to pre-treatment.[3] In this study, the rate of LR-TR non-viable was 41.4 % (12/29), and LR-TR viable was 58.6%, no patient with LR-TR non-evaluation or LR-TR equivocal because we have controlled the imaging standard, technique, and evaluated for imaging base three readers. In the retrospective study, Shropshine. et al assessed the performance of the LI-RADS TRA in 45 patients with 63 lesions from 2006 to 2016, the results showed that the positive predictive value of the LR-TR viable was 86%-96%, and accuracy was 60%-65% in predicting incomplete tumor necrosis; the negative predictive value of the LR-TR nonviable was 81%-87%, and accuracy was 67%-71% to predicting complete tumor necrosis [7]. In the retrospective study of Huh et al (2021), they used LR-TR algorithm attempt to assess the imaging responses after the first time for transarterial embolization compare with Histopathology in 151 HCC base 2 readers, the sensitivity and specificity of CT LR-TR viable were 53.7-56.7% and 96.4-98.8%, the sensitivity, and specificity of CT LR-TR Non-viable were 31.3-34,3% and 95-96% [8].

Pre-treatment liver tumor characteristics (location, size, and morphology) affect treatment options and post-treatment outcomes, which affect the patient's survival time. According to Duong Minh Thang (2008), performing c-TACE on 72 patients divided into 3 groups based on tumors size: 3-<5cm, 5-10cm, >10cm: the average survival time is 19.8±1.8, months, 22.5±2.5 months, 16.9±1.3 months, respectively. The choice of intervention types and intervention level depends on tumor morphology, according to Thai Doan Ky (2015), for confluent or diffuse liver tumors, the author often chooses non-selective intervention methods, embolizing from the right or left hepatic artery. Using LR-TR criteria, we found that the response rate of the tumor after intervention correlated with the tumor's size, if the tumor was less than 5cm. The higher the tumor size, the higher the tumor-free response rate ($p<0.05$) According to the study of Thai Doan Ky (2015), the response rate of liver tumors in the group of patients with liver tumors ≥8cm in size (58.5%) is statistically significantly lower than in the group of patients with liver tumors less than 8cm in size (81.2%, $p=0.011$) [9]. In the world, there are several studies evaluating the correlation between the treatment response of liver tumors after TACE with tumor location, as the results in a study by Miki (2017), Elsahhar A (2021), which show that right and central lobes tumors have a better liver tumor response rate compared to the left lobes and peripheral regions, this is explained by the right and central liver tumors having higher blood flow. Besides, peripheral and left lobe tumors have smaller vessels and the left hepatic artery is often zigzag, so it is more difficult to access. The level of embolization intervention depends on tumor location, size, blood supply, liver function, and portal vein circulation. The more selective the intervention (selective, ultra-selective, or super-selective), the better the liver tumors response and the lower the tumor recurrence rate [10], [11].

AFP is the most used marker because of its diagnostic value. It also has value in assessing treatment response and monitoring the recurrence. A tumor is treatment-responding is when AFP levels fall by 50% or more or AFP values fall below the normal value (<20ng/ml) [5]. Changes in AFP levels are often correlated with the tumor size change and tumor necrosis level. Our study results are different from those of author Bartnik et al (2022) who studied 99 liver tumors undergoing TACE, with 28/99 (28.28%) cases with AFP > 200 ng/ml before treatment, after embolization, evaluating tumor response by LR-TR criteria between 2 groups, the rate of LR-TR tumor-free group < 200 ng/ml was 43.66% (31/71), and in the group with AFP > 200 ng/ml was 28.6% (8/28), the rate of LR-TR and tumor in the group < 200 ng/ml was 50.7% (36/71), and the group > 200 ng/ml is 64.3%, the difference between the 2 groups is statistically significant with $p<0.05$. The reason for this difference is that in our study group, AFP group was divided into 3 groups (less than 20 ng/ml, from 20-400 ng/ml, and > 400 ng/ml) in which the majority were found in the patient in group 2 and group 3, different from the author's study subjects [12]. In the author Riaz study in 2009, there was a correlation between the liver tumor response with WHO and EASL criteria and the post-embolization

AFP response, specifically, the cases of no tumor had a high AFP response (9/12), if the tumor is still active, the AFP response rate drops to 50%, besides, the cases responding to AFP usually have a longer average survival time than the cases with no response group (15 months with 5.3 months), the author believes that AFP is a quick, simple test that does not depend on the reader like radiographic imaging in assessing treatment response as well as long-term prognosis [5].

As we all know, the purpose of LIRADS is to set standards for the selection and screening of the risk of tumors becoming HCC, besides developing a set of criteria for assessing response to treatment on CT /MRI. Many studies have proved that LR-TR has a high value in assessing the response to local treatment, compared with other standards such as post-treatment pathology, angiography, or continuous post-treatment follow-up.

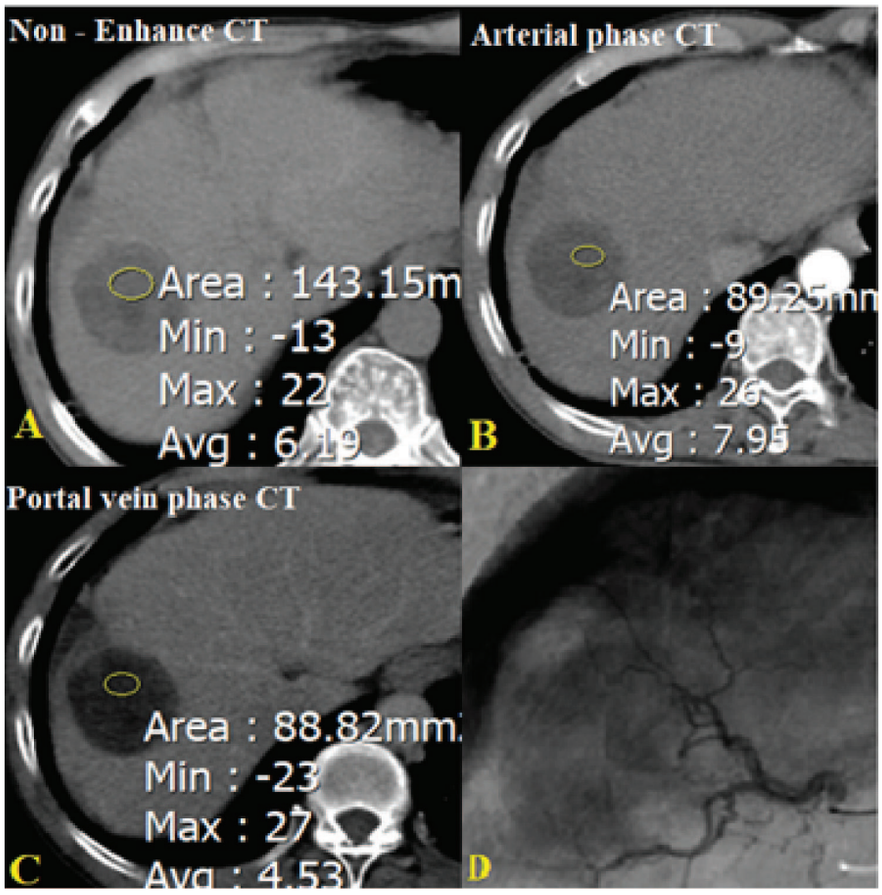

Fig. 1. *56-year-old male with hepatocellular carcinoma who underwent drug-eluting beads transarterial chemoembolization (DEB-TACE). CT imaging post-TACE in 2 months, non-contrast enhancement (A) showed light hyper dense, arterial phase (B) showed no enhancement (similar the Non-enhance CT), portal vein phase (C) demonstrate a washout sign. In the DSA imaging of the second TACE with super selective intervention confirmed hypervascular in tumor (D). The categorized as LR-TR Viable.*

V. CONCLUSION

In conclusion, our retrospective study of 29 patients with hepatocellular carcinoma (HCC) who underwent treatment base drug-eluting beads transarterial chemoembolization (DEB-TACE) shows that the LI-RADS Treatment Response algorithm v2018 on CT performs an easy-to-use, clinically relevant, and useful for vascular interventionists.

REFERENCES

1. Raoul J-L, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. *Cancer Treatment Reviews*. 2019;72:28-36. doi:10.1016/j.ctrv.2018.11.002
2. Recchia F, Passalacqua G, Filauri P, et al. Chemoembolization of unresectable hepatocellular carcinoma: Decreased toxicity with slow-release doxorubicin-eluting beads compared with lipiodol. *Oncology Reports*. 2012;27(5):1377-1383. doi:10.3892/or.2012.1651
3. Chernyak V, Fowler KJ, Kamaya A, et al. Liver Imaging Reporting and Data System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. *Radiology*. 2018;289(3):816-830. doi:10.1148/radiol.2018181494
4. Hoang N. Clinical and paraclinical characteristics and results of liver resection to treat hepatocellular carcinoma after TACE. Thesis Doctor of Medicine, Hanoi Medical University. 2018.
5. Riaz A, Ryu RK, Kulik LM, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2009;27(34):5734-5742. doi:10.1200/JCO.2009.23.1282
6. Kim DW, Choi SH, Lee JS, Kim SY, Lee SJ, Byun JH. Interreader Reliability of Liver Imaging Reporting and Data System Treatment Response: A Systematic Review and Meta-Analysis. *Diagnostics (Basel, Switzerland)*. 2021;11(2):237. doi:10.3390/diagnostics11020237
7. Shropshire EL, Chaudhry M, Miller CM, et al. LI-RADS Treatment Response Algorithm: Performance and Diagnostic Accuracy. *Radiology*. 2019;292(1):226-234. doi:10.1148/radiol.2019182135
8. Huh J, Kim B, Lee JH, et al. Added Value of CT Arterial Subtraction Images in Liver Imaging Reporting and Data System Treatment Response Categorization for Transcatheter Arterial Chemoembolization-Treated Hepatocellular Carcinoma. *Investigative Radiology*. 2021;56(2):109-116. doi:10.1097/RLI.0000000000000714
9. Thai Doan Ky. Study on treatment results of hepatocellular carcinoma by DEB-TACE. Thesis of Doctor of Medicine, Research Institute of Clinical Medicine and Pharmacy 108.; 2015.
10. Miki I, Murata S, Uchiyama F, et al. Evaluation of the relationship between hepatocellular carcinoma location and transarterial chemoembolization efficacy. *World Journal of Gastroenterology*. 2017;23(35):6437-6447. doi:10.3748/wjg.v23.i35.6437
11. Elsahhar A, Abdelwahab SM, Nasser HM, Hassan MS. Assessment of the relationship between hepatocellular carcinoma location and its response to transarterial chemoembolization. *Egyptian Journal of Radiology and Nuclear Medicine*. 2021;52(1):220. doi:10.1186/s43055-021-00601-2
12. Bartnik K, Podgórska J, Rosiak G, Korzeniowski K, Rowiński O. Inter-observer agreement using the LI-RADS version 2018 CT treatment response algorithm in patients with hepatocellular carcinoma treated with conventional transarterial chemoembolization. *Abdominal Radiology*. 2022;47(1):115-122. doi:10.1007/s00261-021-03272-9

Correspondent: Le Duc Nam. Email: namlerad@gmail.com
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